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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,122	09/29/2005	Charles R. Cantor	701586-53303	1567

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,122	CANTOR ET AL.	
	Examiner	Art Unit	
	Kenneth R. Horlick	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14, and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is confusing because it depends from canceled claim 13. Correction is required.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-12, 14, 16, 17, 19, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren et al. (US 2002/0064779) in view of Michnick et al.

These claims are drawn to a method comprising: exposing a target nucleic acid to a first complementation molecule and a second complementation molecule, wherein the first molecule comprises a first polypeptide portion coupled to a first probe portion,

and the second molecule comprises a second polypeptide portion coupled to a second probe portion, wherein upon binding of the first and second probe portions to first and second sites in close proximity on the target nucleic acid, the first and second polypeptide portions of the molecules interact and form an assembled complementation complex which is then detected, wherein the first and second probe portions are nucleic acids or nucleic acid analogues. Claims 21-23 are drawn to a kit comprising a first and second complementation molecule for use in such a method.

Landegren et al. disclose the use of "proximity probes", wherein when first and second binding portions of first and second probes bind to adjacent sites on a target molecule, complementary first and second oligonucleotides attached to said first and second binding portions interact via hybridization and are detected (see Figs. 1-3 and page 1). Note that in paragraph 0010 it is disclosed that the binding portion or moiety may be nucleic acids, and in paragraph 0007 it is disclosed that the target analyte may be a nucleic acid.

While Landegren et al. disclose using complementary nucleic acids on the two binding moieties as the basis for detection of proximate binding sites on a target molecule, they do not disclose the use of polypeptide fragments which form a complementation complex as the basis for detection.

Michnick et al. disclose the use of polypeptide fragments which form a complementation complex as the detection means in a method of detecting proximate binding sites in a target molecule using two binding moieties attached to said polypeptide fragments (see Fig. 1, columns 3-5, column 18, lines 28-30, and columns

23-31). Note especially column 29, line 61 to column 30, line 25, and column 31, lines 2-20, which disclose an embodiment wherein complementation molecules are brought together by attached nucleic acid-binding proteins which simultaneously bind to nearby regions of a target nucleic acid. Michnick et al. also disclose the use of kits in column 37, lines 27-28.

One of ordinary skill in the art would have been motivated to substitute polypeptides which together form a complementation complex for the complementary nucleic acids in the method of Landegren et al. because such a complementation complex was disclosed by Michnick et al., and would have merely provided a predictable and reasonably likely successful alternative detection means (protein complementation) to the complementary nucleic acid means of Landegren et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

3. Claims 4 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren et al. in view of Michnick et al., and further in view of Sodroski et al. (US 5,654,195).

Claim 4 is drawn to the method as described and rejected above, wherein the first and second polypeptides interact in the complementation complex to form an assembled protein which contains a discontinuous epitope, which may be detected with an antibody. Claim 24 is drawn to a kit comprising such a complementation complex.

The teachings of Landegren et al. and Michnick et al. are discussed above. While Michnick et al. broadly suggests the use of any appropriate complementation complexes which can be detected and distinguished from non-complemented fragments, it does not specifically disclose the use of polypeptide fragments which upon complementation form a discontinuous epitope which can be detected with an antibody.

Sodroski et al. disclose that discontinuous epitopes, and antibodies which recognize them, were known in the prior art (see column 12, lines 41-43).

One of ordinary skill in the art would have been motivated to substitute polypeptides which together form a discontinuous epitope recognized by an antibody, for the enzyme-forming polypeptides in the method of Landegren et al. as modified by Michnick et al. because such discontinuous epitopes and antibodies were known and available in the prior art (Sodroski et al.), and would have merely provided a predictable and reasonably likely successful alternative detection means (immunodetection) to the enzymatic detection means of Michnick et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods, and to make and use the claimed kit.

4. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren et al. in view of Michnick et al., and further in view of Lizardi (US 5,854,033).

This claim is drawn to the method as described and rejected above, wherein the target nucleic acid is amplified using rolling circle amplification.

The teachings of Landegren et al. and Michnick et al. are discussed above. These references do not specifically disclose rolling circle amplification.

Lizardi discloses rolling circle amplification (see abstract).

One of ordinary skill in the art would have been motivated to use rolling circle amplification to provide target nucleic acid in the method of Landegren et al. as modified by Michnick et al. because Lizardi disclosed that rolling circle amplification was a good means of providing amplified levels of nucleic acids with multiple benefits/advantages. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

5. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren et al. in view of Michnick et al., and further in view of Stefano et al. (US 6,287,772).

This claim is drawn to the method as described and rejected above, wherein the first and second probes bind to the same sequence in the target nucleic acid such as would form a triplex.

Neither Landegren et al. nor Michnick et al. disclose a proximity probe wherein the two binding portions bind to the same sequence of a target nucleic acid.

Stefano et al. disclose the use of a nucleic acid proximity probe wherein a detection portion on each of two probe strands interacts with the same sequence of a third strand to form a triple helix or triplex (see Figs. 1-11 and columns 2-15).

One of ordinary skill in the art would have been motivated to substitute a triplex detection means for the adjacent binding site means in the method of Landegren et al. as modified by Michnick et al. because such a triplex detection means was disclosed by Stefano et al., and would have merely provided a predictable and reasonably likely successful alternative detection means involving triplex formation. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

6. To the extent that they apply with respect to the above rejections, the arguments of the response filed 03/26/08 have been fully considered, but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary reference Landegren et al. discloses “proximity probes”, wherein the probe portions are nucleic acids, and the complement or detection portions are also nucleic acids, as opposed to polypeptide fragments which form a complementation complex when brought in proximity. Michnick et al. also disclose “proximity probes”, wherein the complement or detection portions are polypeptide

fragments which form a complementation complex when brought in proximity. Thus, this combination of references covers all the elements required in the claimed methods, and the motivation to combine the elements in the required manner would have been the reasonably likely successful and predictable substitution of one detection means (nucleic acid complementation) for another (polypeptide complementation). Thus, it is still believed that a proper case of *prima facie* obviousness has been established, and the rejections are maintained.

7. No claims are free of the prior art.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kenneth R. Horlick whose telephone number is 571-272-0784. The examiner can normally be reached on Monday-Thursday 6:30AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

06/10/08